PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43*bis*.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/HU2004/000062	22.06.2004	23.06.2003

International Patent Classification (IPC) or both national classification and IPC
A61K31/135, A61P25/28

Applicant
EGIS GY GYSZERGY R RT.

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

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Box No. II Priority

1. ☒ The following document has not been furnished:

   ☒ copy of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(a)).

   ☐ translation of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(b)).

   Consequently it has not been possible to consider the validity of the priority claim. This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 16-22

because:

☒ the said international application, or the said claims Nos. 16-22 (no examination as to industrial applicability only) relate to the following subject matter which does not require an international preliminary examination *(specify)*:

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the whole application or for said claims Nos. -

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	4,7,8
	No:	Claims	1-3,5,6,9-22
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-22
Industrial applicability (IA)	Yes:	Claims	1-15
	No:	Claims	

2. Citations and explanations

see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Subject-matter excluded from international preliminary examination (Rule 67.1(iv) PCT)

Claims 16-22 are directed to a method for the treatment of the human or animal body by therapy and, thus, relates to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated under Section V with respect to industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Clarity (Article 6 PCT)

Present claim 3 is not clear, because in contrast to the teaching of the application it is directed to the preparation of pharmaceutical compositions having chronical neurodegenerative effect. Therefore, the search and the examination will be based in this respect on the preparation of pharmaceutical compositions for the treatment of chronical neurodegenerative disorders (cf. page 5).

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

D1: WO 03/007926 A (EGYT GYOGYSZERVEGYESZETI GYAR ; LEVAY GYOERGY (HU); GACSALYI ISTVAN (H) 30 January 2003 (2003-01-30)

D2: WO 02/43726 A (ORION CORP ; MAEKI IKOLA OUTI (FI)) 6 June 2002 (2002-06-06)

D3: CAPONNETTO C ET AL: "Protective effect of cyproheptadine in a gerbil model of cerebral ischemia" ITALIAN JOURNAL OF NEUROLOGICAL SCIENCES, MASSON ITALIA EDITORI, MILAN, IT, vol. 12, 1991, pages 59-61, XP002979212 ISSN: 0392-0461

D4: BERENIJI ET AL: "EGYT-3886" DRUGS OF THE FUTURE, BARCELONA, ES, vol. 15, no. 12, 1990, pages 1174-1175, XP000937796 ISSN: 0377-8282

D5: GACSALYI I ET AL: "DIFFERENT ANTAGONISTIC ACTIVITY OF DERAMCICLANE (EGIS-3886) ON PERIPHERAL AND CENTRAL 5-HT2 RECEPTORS" PHARMACEUTICAL AND PHARMACOLOGICAL LETTERS, SPRINGER INTERNATIONAL, BERLIN, DE, vol. 2, no. 6, 1996, pages 82-85, XP002902366

D6: ARMER R E: "INHIBITORS OF MAMMALIAN CENTRAL NERVOUS SYSTEM SELECTIVE AMINO ACIDTRANSPORTERS" CURRENT MEDICINAL CHEMISTRY, BENTHAM SCIENCE PUBLISHERS BV, BE, vol. 7, no. 2, 2000, pages 199-209, XP000937809 ISSN: 0929-8673

1. **Novelty (Article 33(2) PCT)**

Claim 2 on file is directed to the preparation of pharmaceutical compositions *suitable for* the treatment of certain conditions. Due to the term "suitable for" the therapeutic indications defined in claim 2 are not a technical feature per se and do not impart any limitations to the scope of the claim, as any composition comprising a compound of formula I prima facie is to be considered as suitable for the treatment of diseases defined in claim 2.

1.1. The subject-matter of present claims 1-3, 5, 6, 9-22 is not new in the light of D1.
D1 (page 4) discloses deramciclane, derivatives thereof including N-desmethylderamciclane, and salts thereof including the fumarate salt for use in the treatment

(i) of mental disability consequent on stroke

(ii) of Alzheimer disease and dementia.

Thus, the use of deramciclane for achieving a neuroprotective effect was anticipated by therapeutic indication (i) above, whilst the use for the treatment of chronic neurodegenerative disorders was anticipated by therapeutic indication (ii) above.

1.2. The subject-matter of present claims 1-3, 9, 16, 18, 20, 22 is not new in the light of D2.
D2 (page 2-3) discloses deramciclane and salts thereof including the fumarate salt for use in the treatment of Alzheimer disease and dementia. The same reasoning applies as under item 1.1. above.

2. Inventive step (Article 33(3) PCT)

The subject-matter of claims 1-22 of the present application does not involve an inventive step in the light of D3 and D4.
It has been shown with the application on file that deramciclane has antiischemic activity in a gerbil model of cerebral ischemia.
It was known from the closest prior art that several serotonin antagonists, in particular cyproheptadine, are effective in the same gerbil model.
The objective technical problem to be solved in the light of D3 was, therefore, to provide, apart from cyproheptadine, alternative therapeutic agents for the treatment of cerebral ischemia.
D4 disclosing that deramciclane has 5-HT_2 affinity comparable to that of cyproheptadine suggests the use of deramciclane for solving the above technical problem and, thus, to arrive at the invention according to the claims on file.

Conclusion

As long as the claims on file are not clearly delimited from the D1 and D2, for instance in terms of the therapeutic indication, and as long as it has not been shown why the combined teaching of D3 and D4 does not render obvious the invention according to the claims on file neither novelty nor inventive step can be acknowledged.